# The Role and Impact of Extracorporeal Membrane Oxygenation in Critical Care

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ABSTRACT: Use of extracorporeal membrane oxygenation (ECMO) has been exponentially increasing over the last decade and is now considered a mainstream lifesaving treatment modality in critical care medicine. However, the need for physician education, training, and experience remains imperative. Although ECMO has traditionally been used in end-stage lung disease and circulatory collapse, it is being adopted for use in right heart failure, as a bridge to heart and lung transplantation, and as rescue therapy for both sepsis and post-organ transplantation. The following article discusses indications, management, complications, and challenges of ECMO as well as our experience at the Houston Methodist DeBakey Heart & Vascular Center.

#### INTRODUCTION

Hypoxic respiratory failure and/or cardiogenic shock are two of the most difficult cases that can present in the intensive care unit (ICU) and put patients at high risk for ICU mortality. Hypoxic respiratory failure in the presence of bilateral pulmonary infiltrates without evidence of left heart failure is a hallmark of acute respiratory distress syndrome (ARDS). There are an estimated 140,000+ cases of ARDS in the United States annually, with a mortality rate between 22% and 41%.1 Although the ARDSnet study demonstrated a decrease in mortality with lower tidal volumes,2 there are limits to decreases in ventilator volumes and oxygen concentrations that one can administer and still maintain adequate blood gases. In the presence of severe ARDS, compromised airway pressures and oxygen concentrations can exacerbate the inflammatory cascade with barotrauma, volutrauma, and oxygen toxicity, thus prolonging pulmonary recovery. The CESAR trial (conventional ventilator support vs. extracorporeal membrane oxygenation for severe adult respiratory failure) demonstrated a potential benefit with extracorporeal membrane oxygenation (ECMO) for the aggressive treatment of ARDS and has expanded the use of ECMO nationwide.3

The use of cardiopulmonary bypass technologies such as ECMO allows for more aggressive lung rest strategies and cardiovascular support than could be provided otherwise. Depending on the choice of cannulation techniques, ECMO can deliver purely respiratory support, respiratory support with right ventricular support, and full cardiopulmonary support. Today, with careful patient selection, ECMO is used as a rescue therapy to allow for recovery or bridge to transplant for hypoxic respiratory failure and severe refractory cardiogenic shock. The following review discusses the role and impact of ECMO in critical care delivery as well as the challenges and experience at our own institution.

#### THE ROLE OF ECMO IN CARDIOGENIC AND RESPIRATORY FAILURE

# Role in Circulatory Failure

Acute circulatory failure is defined as inadequate tissue perfusion despite adequate intravascular volume and maximal medical management, with systolic blood pressure < 90 mm Hg, pulmonary wedge pressure > 15-20 mm Hg, central venous pressure > 12 mm Hg, cardiac index < 1.8-2.0 L/min/m², and poor central venous oxygen saturation even after inotropic support or placement of an intra-aortic balloon pump.

Typical indications for ECMO support in cardiac patients include (1) cardiogenic shock, (2) postcardiotomy shock, (3) periprocedural support, (4) post heart transplant, (5) bridge to destination/left ventricular assist device (LVAD), (6) bridge to heart transplant, and (7) extracorporeal cardiopulmonary resuscitation (E-CPR), (Table 1).<sup>4</sup>

In these patients, ECMO is used as a modified cardiopulmonary bypass, and venoarterial cannulation (VA-ECMO) is performed using either a peripheral or central approach.<sup>5</sup> This type of mechanical support drains blood from the right atrium and directs it to the arterial system, thus reducing preload and increasing aortic flow and end-organ perfusion.

The goal for ECMO placement in cardiogenic shock is to support the patient as a bridge to recovery, destination, or surgery by stabilizing systemic circulation until myocardial recovery. In patients with end-stage heart failure or failure to recover, ECMO is considered as a bridge to LVAD therapy<sup>6</sup>; it also can be used as a bridge to surgery or procedure in patients with pulmonary embolism, for example, until emergent embolectomy.<sup>7</sup> Another use of VA-ECMO is E-CPR to assist in

INDICATIONS FOR ECMO SUPPORT	SYMPTOMS
Cardiogenic shock	Acute coronary syndrome Refractory arrhythmia Acute fulminant myocarditis Acute right ventricular failure Acute pulmonary embolism <sup>7</sup> Postpartum cardiomyopathy Drug overdose leading to severe myocardial depression
Postcardiotomy shock	Inability to separate from cardiopulmonary bypass
Periprocedural support	High-risk percutaneous coronary intervention  Acute right ventricular failure after insertion of left ventricular assist device (LVAD)
Post heart transplant	Primary graft failure Hyperacute rejection following heart transplant
Bridge to destination/LVAD <sup>6</sup>	Class IV/stage D heart failure Chronic cardiomyopathies
Bridge to heart transplant	
Extracorporeal cardiopulmonary resuscitation	Time from cardiac arrest to initiation of ECMO flow < 30 min
Table 1.	

restoring circulation during cardiac arrest. In this setting, data shows improved in-hospital survival and less major neurological impairment when E-CPR is used in conjunction with algorithmic life-support strategies.<sup>8</sup> Venoarterial ECMO can be effectively used as a short-term bridge to heart transplant therapy in patients with decompensated chronic heart failure on the verge of circulatory collapse and multisystem organ failure.<sup>9,10</sup>

Indications and related symptoms of extracorporeal membrane oxygenation (ECMO) support.

## Role in Respiratory Failure

ECMO is typically used for respiratory support in the following settings: (1) acute respiratory distress syndrome (viral or bacterial pneumonia, aspiration, acute alveolar proteinosis); (2) assistance with lung rest (e.g., for traumatic lung injury or pulmonary contusion, smoke inhalation)<sup>11,12</sup>; (3) severe acute asthma (persistent bronchospasm with  $CO_2 > 80$ ); (4) pulmonary hemorrhage/diffuse alveolar hemorrhage; (5) bridge to lung transplant<sup>13,14</sup>; (6) primary graft dysfunction after lung transplant<sup>15,16</sup>; and (7) pneumonectomy.<sup>4</sup>

Both venovenous (VV) and VA-ECMO can be used in patients with acute respiratory failure, and ECMO can be

used for both hypoxemia and hypercarbia (Figure 1). Since the CESAR trial supporting ECMO for ARDS patients,<sup>3</sup> multiple studies have been done to further evaluate the outcomes of ECMO use in ARDS because questions remained as to whether or not ECMO should be used as rescue therapy or more proactively as protective mechanical support. ECMO has been successfully used for lung rest in patients with inhalation injuries and traumatic lung injuries.<sup>11</sup> Outcomes in patients with severe traumatic lung injury treated with ECMO appear to be better than those in patients treated with conventional modalities.<sup>12</sup>

#### Emerging Role of ECMO in Other Disease Processes

More recently, ECMO has been used as an extended bridge to lung transplant for end-stage lung disease patients who are on the transplant waiting list and presenting with acute respiratory failure. 13,14 Use of ECMO has been studied after lung transplantation for primary graft dysfunction, and it continues to be the most common indication after transplant. 15 ECMO is used as rescue therapy in these patients, and it is required in about 5% of transplant procedures. 16

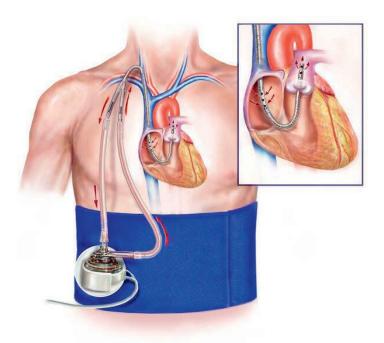


Figure 1.
The PROTEK Duo veno-venous cannula (CardiacAssist, Inc.) provides venous drainage and reinfusion of blood through an internal jugular vein while on ECMO support.

Profound cardiogenic shock may occur in severe sepsis,<sup>17</sup> and ECMO has been successfully used as a salvage therapy in the pediatric population. Lately, it has also been used in the adult population, and early outcomes appear promising.<sup>18,19</sup>

#### ISSUES, CHALLENGES, AND COMPLICATIONS

# Cannulation and Associated Challenges

Cannulation for ECMO is one of the major sources of morbidity. Although a full surgical review of cannulation is out of the scope of this article, the main goal of ECMO cannulation is to provide the least traumatic and most durable and simplified method of delivering blood to and from the pulmonary circuit. <sup>20,21</sup> In peripheral VA-ECMO, the femoral artery is the most common cannulation site. Oxygenated blood is delivered to the aorta via the femoral artery in retrograde fashion and competes with native antegrade circulation generated by the heart. Potential problems include separate perfusion of the upper and lower parts of the body, left ventricular distention, reduced coronary flow, and pulmonary edema due to the increased afterload produced by ECMO. <sup>20</sup> One specific complication is lower limb ischemia due to partial occlusion of the femoral arterial lumen by the cannula. This

can be overcome by using a reperfusion circuit inserted into the femoral artery distal to the cannula or by cannulating the tibial artery to perfuse the lower limb.

Central VA-ECMO is usually the last resort to salvage full cardiopulmonary collapse because it has associated aortic and sternotomy-related complications.

In VV-ECMO, one method uses the femoral approach by draining the blood with a shorter cannula from the inferior vena cava and returning it directly to the right atrium (Figure 2). Although recirculation can be more problematic, this technique avoids neck vessel cannulation and injury.<sup>20</sup> Another method uses the right internal jugular approach with the Avalon ELITE (MAQUET Holding B.V. & Co.) or Protek Duo (CardiacAssist, Inc.) cannula (Figure 1). This method has several benefits, including reduced bleeding risk since only one vessel is punctured, a lower rate of recirculation, and ease of mobilization.<sup>22</sup> In inadequate flow



Figure 2.
Typical femoral veno-venous cannulation.

provision, as patients often have supraphysiological cardiac output, adding a second drainage cannula may ameliorate flow but carries additional risks.<sup>20</sup>

#### **Bleeding**

Bleeding is the most frequent and serious complication associated with ECMO support<sup>23</sup> and can stem from heparin overdose, thrombocytopenia, platelet dysfunction, coagulopathy, acquired von Willebrand syndrome, and hyperfibrinolysis.<sup>24</sup> Bleeding may occur at the site of cannula insertion, lung, gastrointestinal tract, mouth, nose, thoracic or abdominal cavity, and brain. These ECMO-related bleeding complications can be managed successfully with surgical and endoscopic approaches.<sup>25</sup> There is a delicate balance between bleeding and thrombosis in the setting of ECMO; therefore, better control of the activated partial thromboplastin time may improve patient outcomes.<sup>23</sup>

# Infection

There is a 10% to 12% prevalence of hospital-acquired infections during ECMO, and they are likely to occur more frequently than with other critically ill patients; this is particularly true of ventilator-associated pneumonia. The most important risk factor for infection is the duration of the ECMO run. Other risk factors include the severity of illness; the high risk of bacterial translocation from the gut; ECMO-related impairment of the immune system; and microbial colonization of catheters, ECMO cannula, and the oxygenator.<sup>26</sup>

# Ventilation Strategies

During VV-ECMO, mechanical ventilation is required because the blood flow rate with ECMO is usually not enough, and in a hyperdynamic status, a substantial proportion of blood is still passed via the native lung since it has not first passed through the artificial lung. In addition, the lung should be mildly ventilated and kept open because complete collapse of the lung may delay its recovery.<sup>27</sup> In a study by Schmidt et al., higher positive end-expiratory pressure levels during the first 3 days of ECMO support were associated with lower mortality.<sup>28</sup>

In another study by Schmidt et al., 77% of ECMO centers reported "lung rest" as the primary goal of mechanical ventilation, while a tidal volume of < 6 mL/kg was targeted in 76% of the centers. <sup>29</sup> Another component of protective ventilation is a low respiratory rate (between 3 and 5 breaths/min), with the rationale being to rest the lung by reducing its motion with peak airway pressure limited to between 35 and 45 cmH<sub>2</sub>O. To limit pulmonary oxygen toxicity, the ventilator FiO<sub>2</sub> should be reduced to a minimum to keep oxygen saturation > 85%. <sup>30</sup>

Prolonged controlled ventilation without diaphragmatic contraction may result in severe atrophy and increased duration of ventilatory support. The pressure-assisted mode with spontaneous diaphragm contraction should therefore be used as soon as possible. Also, the adverse effects of deep sedation and paralysis, including bradycardia, ICU-acquired paresis, and ventilator-associated pneumonia, pose valid concerns.<sup>27</sup> Evidence is accumulating on the use of ECMO in awake, spontaneously breathing patients; for example, ECMO use improved survival in patients awaiting lung transplantation compared to other bridging strategies.<sup>29</sup>

The ongoing EOLIA trial (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) will test the efficacy of early VV-ECMO in patients with severe ARDS. It is expected to overcome weaknesses of previous trials (i.e., the CESAR trial) with better control of mechanical ventilation in the control group, better timing of the ECMO onset, and strict adherence to randomization procedures.<sup>20</sup>

# Hepatic, Renal, and Neurologic Involvement

Acute kidney injury is frequently observed in patients undergoing ECMO and may be related to several conditions derived from or associated with this therapy that are hemodynamic, hormonal, and inflammatory in nature. Despite the knowledge gaps about the relationship between ECMO and kidney function, there is a need to provide renal support therapy during ECMO. In particular, renal replacement therapy is usually required for management of fluid overload and removal of inflammatory mediators.<sup>31</sup>

A proportion of patients needing ECMO have early elevation of liver enzymes that usually improves over days. The prognostic implications are not evident. However, in patients undergoing ECMO following cardiovascular surgery, liver function predicts survival. 32 The rates of intracerebral hemorrhage, acute ischemic stroke, and seizure among patients receiving ECMO were each approximately 4%, but nearly 11% of patients treated with ECMO had one of these neurologic complications. 33 Furthermore, patients with cardiac arrest and shock had significantly higher rates of neurologic morbidity and mortality than those without these conditions.

# Immobilization and Rehabilitation

Patient immobility during ECMO support can result in physical impairment that may lead to prolonged hospitalization and poor functional outcomes for ECMO survivors.<sup>34</sup> Early intervention with physical therapy may decrease duration of hospitalization and improve functional outcomes for ECMO-supported patients. Active physical therapy, including ambulation, can be achieved

safely and reliably in ECMO patients when an experienced, multidisciplinary team is used.

#### Pressure Ulcers

Patients receiving ECMO are at a greater risk of developing skin breakdown. Contributing factors include poor perfusion, hemodynamic instability with vasopressor use, ischemia due to capillary occlusion, reperfusion injury, impaired lymphatic drainage, accumulation of metabolites, comorbid conditions, poor nutritional status, and immobilization due to the fear of accidental decannulation. Implementation of an evidence-based skin breakdown bundle has been demonstrated to be effective in reducing skin breakdown.<sup>35</sup>

## **Nutrition**

Studies showed that enteral nutrition in patients receiving either VA- or VV-ECMO is well tolerated, provides adequate nutrition, is cost effective, and is without complications compared with parenteral nutrition, which is primarily used in patients with an open chest.<sup>36</sup> However, in a retrospective study by Pettignano et al., patients received inadequate nutritional support, with only 55% of their nutritional targets achieved while receiving ECMO.<sup>37</sup> Optimal nutritional support should be a major goal and requires careful consideration to prevent complications of malnutrition.

#### Staffing Model and Cost

The ECMO team consists of the physician performing the cannulation along with an intensivist, bedside nurse, respiratory therapist, perfusionist, and specialist.<sup>38</sup> The Extracorporeal Life Support Organization (ELSO) defines the specialist as "the technical specialist trained to manage the ECMO system and clinical needs of the patient on ECMO under direction and supervision of an ECMO-trained physician."<sup>39</sup>

ECMO is a highly resource-demanding procedure. The major portion of the cost is related to personnel resources, diagnostic and laboratory tests, radiology, ICU and operating room procedures, medications, and blood product transfusion. Studies show a large variation in the cost of ECMO over multiple cost categories. 40,41 For example, a recent study showed that an average ECMO procedure costs \$73,122, whereas an average ECMO patient had a total hospital cost of \$210,142.42

# Social Concerns, Ethical Dilemmas, and Survivors' Support

The family should be informed with a defined time and goals of support along with transparent updates. This trust and alliance with the family is often achieved with multiple multidisciplinary family meetings involving primary physicians, social workers, spiritual advisors, psychologists, palliative-care specialists, immediate-care providers, and members of the hospital ethics committee. <sup>43</sup> Multidisciplinary evidence-based interventions should be implemented early on to improve quality of life by helping with the physical, psychological, and social problems that ECMO survivors experience. <sup>44,45</sup>

# Rapid Expansion of ECMO Programs in the United States

One analysis before and after the H1N1 epidemic in 2009 showed that the rate of ECMO increased 433%—from 11.4 cases per million U.S. adult discharges in 2006 to 60.9 cases in 2011.<sup>46</sup> This trend continues to rise and is expected to rise at least in the near future.

# EXPERIENCE AT THE HOUSTON METHODIST DEBAKEY HEART & VASCULAR CENTER

At the Houston Methodist DeBakey Heart & Vascular Center, the most important lesson we learned was that it takes a multidisciplinary team to improve quality and reduce mortality in the ECMO patient population. A review of data shows that the following 12 endeavors played a significant role in achieving substantial results.

- Development of selection criteria. The backbone of our success is the development of inclusion and exclusion criteria in view of evidence-based medicine (Table 2). These criteria play a major role in determining whether or not a patient should receive ECMO treatment.
- 2. Pharmacy-managed anticoagulation protocol. Bleeding is the major limiting factor in the success of ECMO programs.<sup>23-25</sup> To effectively avoid this complication, a dedicated pharmacy-managed anticoagulation protocol was developed with a target activated partial thromboplastin time (aPTT) of 60 to 80 seconds in most cases (Figure 3). A STAT aPTT/PT blood draw is done when initiating ECMO and repeated every 4 hours to obtain therapeutic levels of aPTT. The criteria is based on calculating the ratio of actual body weight (ABW) to ideal body weight with the cut-off ratio of 1.2, where ABW is used if the ratio is above 1.2, or to calculate the dosing weight with the formula shown in Figure 3. The decision to deviate from the protocol is made with the consent of the intensivist and surgical service and in conjunction with other lab values of prothrombin time/ international normalized ratio, hemoglobin/hematocrit, and platelets, along with the overall clinical situation.
- Continuous ECMO care. Another core reason for our success was the implementation of 24/7 ECMO care both at the bedside and as liaison care between clinical teams. Only

ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
Age > 80 years	Local skin infection at the cannulation site
Irreversible multisystem organ failure	Known bilateral DVT of femoral veins
SOFA score > 11	Severe PVD
Contraindication to anticoagulation	Previous stent that could preclude access
Unrecoverable cardiac condition and not a candidate for VAD or transplant	ICH or severe brain damage
Unrecoverable respiratory condition and not a candidate for transplant	> 7 days of ventilation
Active life-limiting conditions (disseminated malignancy)	Obesity
Cardiac arrest with asystole persisting for > 30 min	

#### Table 2.

Exclusion criteria for extracorporeal membrane oxygenation use at Houston Methodist DeBakey Heart & Vascular Center. Relative contraindications will change according to circumstances or context. SOFA: Sequential Organ Failure Assessment, a score that predicts ICU mortality based on lab results and clinical data; VAD: ventricular assist device; DVT: deep vein thrombosis; PVD: peripheral vascular disease; ICH: intracerebral hemorrhage

highly experienced nurses with adult CCRN certification and ELSO training were eligible to apply and undergo a detailed interview process.

- 4. **Ventilator management protocol.** A ventilator management protocol was developed to minimize fluid intake and incorporate a lung protective strategy, which includes maintaining a low tidal volume and optimum high positive end-expiratory pressure (PEEP).<sup>27,29</sup> An emphasis was placed on the pressure volume curve to obtain an optimum PEEP<sup>28</sup> and protect the lungs from oxygen toxicity by lowering the target oxygen saturation to > 80%.<sup>30</sup>
- 5. VV-ECMO weaning protocol. In patients with respiratory failure, our protocol uses a stepwise method to first wean FiO<sub>2</sub> on the ventilator to 40% followed by weaning of FiO<sub>2</sub> on ECMO with target oxygen saturation to 90%. Once the patient can tolerate a lower FiO<sub>2</sub> on the ventilator and ECMO, the flow on ECMO can be weaned to < 2.5 L. Cannulation for ECMO can be discontinued if the patient sustains good hemodynamics and oxygen saturation.</p>
- 6. VA-ECMO weaning protocol. For patients in cardiogenic shock, we advocated a right upper extremity arterial line and pulmonary artery catheter. Patients were discontinued from ECMO if they could tolerate a flow less than 2.5 L/min with the following parameters: central venous pressure < 18 mm Hg; pulmonary artery occlusion pressure < 20 mm Hg; cardiac index > 2.4 L/min; mean arterial pressure > 60 mm Hg; and left ventricular ejection fraction > 30%.

- Intensivist ownership of ECMO management. With their 24/7 ICU availability, intensivists have been designated to coordinate and execute a daily plan for ECMO after multidisciplinary rounds with the surgeon, pulmonologist, cardiologist, ECMO specialist, perfusionist, and other available services.
- 8. **Development of ECMO admission order set.** A protocol order set was developed and fed into the hospital's electronic medical record system to cover all required aspects of ECMO management, including but not limited to hemodynamic monitoring, nutrition, ventilator orders, laboratory orders, and all required consults.
- 9. Physical-therapy-driven early ambulation. Early extubation is a priority for patients on VV-ECMO, particularly those with an upper body cannula. Physical therapy, including airway clearance, upper and lower extremity exercises, and mobilization (as tolerated), begins during the weaning process to minimize the need for sedation and facilitate early ambulation and extubation.
- 10. Fewer blood draws. We set a hemoglobin level goal of > 10 g/dL, which was achieved by maximizing efforts to decrease bleeding and minimizing blood draws through consolidation of all daily required draws.
- 11. Mandatory ethics and palliative consults on all ECMO patients. ECMO can be extremely overwhelming for

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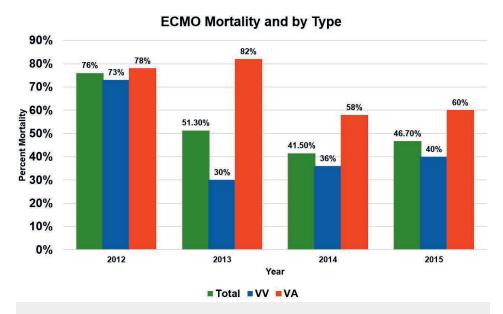


Figure 4.

Decrease in mortality at the Houston Methodist DeBakey Heart & Vascular Center achieved by instituting a multidisciplinary team approach. VV: venovenous; VA: venoarterial

families, and the initiation of ECMO often prompts ethical questions and/or discordance among families, providers, and even different consulting teams. <sup>43</sup> For these reasons, consults from our ethics and palliative services were made mandatory from day zero of ECMO initiation, with a default consult built into the initial order set in our electronic medical record system.

12. Process for hospice. Every patient deserves dignity at the end of life. In the case of unsuccessful ECMO treatment, official arrangements with a hospice provider are made to help ease the transition for patients and families.

Implementing these steps over the course of 3 years yielded remarkable results, with total ECMO mortality dropping from 76% in 2012 to 46.7% in 2015 (Figure 4). Although nationwide mortality remains stable, <sup>47</sup> our institution was able to show a marked decrease in mortality by implementing this comprehensive multidisciplinary approach.

#### CONCLUSION

Despite various challenges, ECMO is a vital lifesaving modality in patients with respiratory and cardiorespiratory failure. New frontiers are demonstrating the benefit of ECMO in right heart failure and as a bridge and rescue modality in lung and heart transplant, and it has recently been used for patients in cardiogenic shock due to severe sepsis. We are witnessing more and more institutions adapting its use despite the challenges of cost and staff training. Although the institutional learning curve may take a few years, significant reductions in mortality can be achieved in high-risk patients who may otherwise not survive.

# $Conflict\ of\ Interest\ Disclosure:$

The authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest Statement and none were reported.

#### Keywords:

extracorporeal membrane oxygenation, ECMO, cardiogenic shock, acute respiratory distress syndrome, ARDS, lung transplant, heart transplant, right heart failure, sepsis.

#### **KEY POINTS**

- ECMO is a viable rescue therapy in acute lung failure and circulatory collapse.
- ECMO has been indicated for use in right heart failure, as a bridge to heart and lung transplantation, and as a rescue therapy after heart and lung transplantation.
- There is an emerging role of ECMO in cardiogenic shock related to severe sepsis.
- Use of ECMO has posed new challenges for institutions and requires training and education of staff to address these complications.
- A successful ECMO program in any institution requires a multidisciplinary approach that includes intensivists, surgeons, perfusionists, pharmacists, ECMO specialist nurses, bedside nurses, palliative care services, physical therapists, an ethics team member, and other consulting services.
- Family involvement, education, and consent is critical at every step of the treatment process.
- ECMO programs across the United States continue to rise and are expected to continue this trend in the near future.
- Our experience at the Houston Methodist DeBakey Heart & Vascular Center reaffirmed the need for engagement of the entire institution in a multidisciplinary team approach to ensure a successful ECMO program.

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